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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/510,908	08/01/2005	Bernd Kuhn	Le A 36 031	7332

35969 7590 07/03/2008

Barbara A. Shimci
Director, Patents & Licensing
Bayer HealthCare LLC - Pharmaceuticals
555 White Plains Road, Third Floor
Tarrytown, NY 10591

EXAMINER	
LAU, JONATHAN S	

ART UNIT	PAPER NUMBER
1623	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/510,908	KUHN ET AL.	
	Examiner	Art Unit	
	Jonathan S. Lau	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is responsive to Applicant's Amendment and Remarks, filed 25 Mar 2008, in which claims 3-6 and 8-9 are amended to correct improper multiple dependency and claims 2, 7 and 10 are amended to correct minor informalities.

This application is the national stage entry of PCT/EP03/03327, filed 31 Mar 2003; and claims benefit under 35 USC 119(a-d) of foreign priority document GERMANY 10215942.4, filed 11 Apr 2002; currently an English language translation of this foreign priority document is not of record.

Claims 1-10 are pending in the current application.

The following are new or modified rejections. The following rejections are not necessitated by Applicant's Amendment.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-3 are rejected under 35 U.S.C. 102(a) as being aniticpated by Mauler et al (J. Pharmacol. Exp. Ther., 2002, of record – Published online June 13, 2002. Mailed June 14, 2002).

Mauler teaches a composition comprising 1% BAY 38-7271 (compound I) and a cyclodextrin. See paragraph bridging the columns of page 362. The composition is suitable for continuous infusion. This composition is prepared by dissolving BAY 38-7271 in ethanol and adding a 10% solution of cyclodextrin. The reference is silent regarding the solvent of the cyclodextrin. However, for a physiological solution, if the solvent is not named, it would be expected to be water.

Response to Applicant's Remarks:

Applicant's Remarks, filed 25 Mar 2008, have been fully considered and found persuasive regarding the filing date of the instant applicant, 31 Mar 2003, and the filing date of foreign priority document GERMANY 10215942.4, filed 11 Apr 2002. However, currently an English language translation of this foreign priority document is not of record.

Applicant cannot rely upon the foreign priority papers to overcome this rejection under 35 U.S.C. 102(**a**) because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4, 8 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mauler et al (J. Pharmacol. Exp. Ther., 2002) in view of Szabo et al (J. Pharmacol. Exp. Ther., 2001).

Mauler teaches as set forth above. The reference further teaches that BAY 38-7271 is a cannabinoid receptor agonist with a variety of therapeutic uses. See 1st paragraph at page 359. The compound is deemed similar in activity to other known agonists, such as WIN 55,212-2 and CP 55,940.

As discussed above, one of ordinary skill would expect that the cyclodextrin solvent would be water. However, it may be that this is not the case.

Szabo teaches that an aqueous solution comprising a cyclodextrin is a suitable vehicle for infusing the cannabinoid agonists, WIN 55,212-2 and CP 55,940. See page 820, 2nd paragraph under "Drugs." The reference further notes that other drugs are dissolved in ethanol and saline.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare a composition comprising BAY 38-7271 for infusion using any suitable physiologically solution for administration as taught by Mauler. One of ordinary skill would use a vehicle known to be used for other similar therapeutic compounds, such as the aqueous solution comprising a cyclodextrin, with a reasonable expectation of success. In the absence of unexpected results, it would be further within the scope of the artisan to modify this vehicle with other standard physiological solvents, such as ethanol and/or saline to optimize the characteristics of the composition through routine experimentation. It would be further within the scope of the artisan to optimize the amounts of compound I, cyclodextrin and ethanol in said composition for the intended use.

The instant claims recite a composition comprising compound I and various standard physiological excipients. However, the examiner does not find there to be any evidence of criticality in any particular mix of components.

Response to Applicant's Remarks:

Applicant's Remarks, filed 25 Mar 2008, have been fully considered and found persuasive regarding the filing date of the instant applicant, 31 Mar 2003, and the filing date of foreign priority document GERMANY 10215942.4, filed 11 Apr 2002. However, currently an English language translation of this foreign priority document is not of record.

Applicant cannot rely upon the foreign priority papers to overcome this rejection under 35 U.S.C. 103 based on the reference Mauler applicable under 35 U.S.C. 102(**a**)

because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Applicant remarks that the composition containing said compound and cyclodextrin unexpectedly leads to uniform concentrations of the compound. However, it is known in the prior art that cyclodextrin is used to increase aqueous solubility, stability, and bioavailability of lipophilic drugs such as the cannabinoid receptor agonist THC by forming inclusion complexes. See Jarho et al. (Life Sciences, 1998, 63(26), pPL381-PL384, cited in PTO-892). One of skill in the art would expect that a compound with increased aqueous solubility, stability, and bioavailability would be present in uniform concentrations because non-uniform concentrations in solution are commonly related to poor solubility of solutes, as one well-known example of non-uniform concentration is seen in the process of precipitation of an insoluble compound out of solution, where the local concentration of the compound at the point of the precipitation is not uniform with the concentration in bulk solution.

Applicant asserts that Szabo is not suitable for combination with Mauler because Szabo is drawn to injection in bolus dosages. However Szabo also teaches injection by infusions (page 820, 2nd paragraph under "Drugs.")

Applicant remarks that the compound disclosed by Mauler and the cannabinoid receptor agonists taught by Szabo are not equivalents because the compound of Mauler is structurally unrelated to the cannabinoid receptor ligands known so far, such as those taught by Szabo. However, the context of that statement is regarding ligands of the CB1 receptor, therefore the comparison is drawn to the pharmacological

interaction of a compound and a specific receptor. In this regard, the instant compound is not structurally related to the moieties that result in receptor-binding in the prior art compounds. However, with regard to structural equivalence for determining solubility and formation of inclusion complexes with cyclodextrin, structural relationships are based on principles of physical organic chemistry, such as size of the molecule and polarity of the molecule. In this regard the instant compound is a small organic molecule containing aromatic rings expected to form inclusion complexes with cyclodextrin, as evidenced by Loftsson (Journal of Pharmaceutical Sciences, 1996, 85(10), p1017-1025, provided by Applicant in IDS filed 08 Oct 2004) page 1023, proposed structures of table 6 and table 7. Therefore one of ordinary skill in the art at the time of the invention would have a reasonable expectation that the compound disclosed by Mauler and the cannabinoid receptor agonists taught by Szabo possess similar physical organic characteristics.

Claims 1- 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mauler et al (J. Pharmacol. Exp. Ther., 2002) in view of Szabo et al (J. Pharmacol. Exp. Ther., 2001) and Nakazi et al (Naunyn-Schmiedeberg's Arch. Pharmacol., 2000).

Mauler and Szabo teach as set forth above. The references are silent regarding the pH of the solutions or the use of citric acid.

Nakazi teaches that a citrate buffer (pH 4.8) is a suitable vehicle for cerebral infusion of the cannabinoid agonists, WIN 55,212-2 and CP 55,940. See paragraph bridging pages 20 and 21.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare a composition comprising BAY 38-7271 for infusion using any suitable physiologically solution for administration as taught by Mauler. One of ordinary skill would use a vehicle known to be used for other similar therapeutic compounds, such as the aqueous solution comprising a cyclodextrin, with a reasonable expectation of success. In the absence of unexpected results, it would be further obvious to modify this composition by adjusting it to a suitable pH for cerebral infusion with a citrate buffer with a reasonable expectation of success.

The instant claims recite a composition comprising compound I and various standard physiological excipients. However, the examiner does not find there to be any evidence of criticality in any particular mix of components.

Response to Applicant's Remarks:

Applicant's Remarks, filed 25 Mar 2008, have been fully considered and found persuasive regarding the filing date of the instant applicant, 31 Mar 2003, and the filing date of foreign priority document GERMANY 10215942.4, filed 11 Apr 2002. However, currently an English language translation of this foreign priority document is not of record.

Applicant cannot rely upon the foreign priority papers to overcome this rejection under 35 U.S.C. 103 based on the reference Mauler applicable under 35 U.S.C. 102(a) because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Claims 1-4 and 8-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mauler et al (J. Pharmacol. Exp. Ther., 2002) in view of Szabo et al (J. Pharmacol. Exp. Ther., 2001) and Yamada (US 5,807,337).

Mauler and Szabo teach as set forth above. The references teach the infusion of cannabinoid receptor agonists but are silent regarding the description of the infusion apparatus used in each reference.

It is well known in the art to use an infusion apparatus for the continuous administration of therapeutic agents, and the drug-contacting surfaces are typically plastic. See, for example, Yamada at col 5, lines 15-25.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare the recited composition, as set forth above. It would be further obvious to combine the composition with an infusion apparatus to form a kit for administration of the composition. It would be within the scope of the artisan to select any appropriate apparatus for this utility.

Response to Applicant's Remarks:

Applicant's Remarks, filed 25 Mar 2008, have been fully considered and found persuasive regarding the filing date of the instant applicant, 31 Mar 2003, and the filing date of foreign priority document GERMANY 10215942.4, filed 11 Apr 2002. However, currently an English language translation of this foreign priority document is not of record.

Applicant cannot rely upon the foreign priority papers to overcome this rejection under 35 U.S.C. 103 based on the reference Mauler applicable under 35 U.S.C. 102(**a**)

because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Claims 1-4, 8 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mittendorf et al. (US Patent 6,262,112, issued 17 Jul 2001, cited in PTO-892) in view of Szabo et al (J. Pharmacol. Exp. Ther., 2001, of record).

Mittendorf discloses a pharmaceutical composition comprising the compound (-)-(R)-3-(2-hydroxymethylindanyl-4-oxy)phenyl 4,4,4-trifluorobutane-1-sulfonate (column 199, claim 1 and column 200, claim 5). Mittendorf discloses the compound is a cannabinoid receptor agonist (column 1, lines 23-50). This composition is suitable for administration as a continuous infusion (column 36, lines 55-58). Mittendorf discloses the composition wherein the solvent is aqueous NaCl (column 36, lines 15-20). Mittendorf discloses the compound with suitable excipients and envisions the use of organic solvents as auxiliary solvents if water is used as a diluent (column 37, lines 20-30). Mittendorf discloses the dosage of the compound of 0.01 to 10 mg/kg (column 37, lines 35-37).

Mittendorf does not specifically disclose the excipient cyclodextrin or the ratio of compound to cyclodextrin.

Szabo teaches that an aqueous solution diluted with an 19% cyclodextrin solution is a suitable vehicle for infusing the cannabinoid receptor agonists, WIN 55,212-2 and CP 55,940. See page 820, 2nd paragraph under "Drugs." The reference further teaches that other similar drugs are dissolved in ethanol and saline.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare a composition comprising said for infusion using any suitable physiologically solution for administration as taught by Mittendorf. One of ordinary skill would use a vehicle known to be used for other similar therapeutic compounds, such as the aqueous solution comprising a cyclodextrin, with a reasonable expectation of success. In the absence of unexpected results, it would be further within the scope of the artisan to modify this vehicle with other standard physiological solvents, such as ethanol and/or saline to optimize the characteristics of the composition through routine experimentation. It would be further within the scope of the artisan to optimize the amounts of compound I, cyclodextrin and ethanol in said composition for the intended use.

The instant claims recite a composition comprising compound I and various standard physiological excipients. However, the examiner does not find there to be any evidence of criticality in any particular mix of components.

Response to Applicant's Remarks:

Applicant's Remarks, filed 25 Mar 2008, have been fully considered and not found to be persuasive.

Applicant remarks that the composition containing said compound and cyclodextrin unexpectedly leads to uniform concentrations of the compound. However, it is known in the prior art that cyclodextrin is used to increase aqueous solubility, stability, and bioavailability of lipophilic drugs such as the cannabinoid receptor agonist THC by forming inclusion complexes. See Jarho et al. (Life Sciences, 1998, 63(26),

pPL381-PL384, cited in PTO-892). One of skill in the art would expect that a compound with increased aqueous solubility, stability, and bioavailability would be present in uniform concentrations because non-uniform concentrations in solution are commonly related to poor solubility of solutes, as one well-known example of non-uniform concentration is seen in the process of precipitation of an insoluble compound out of solution, where the local concentration of the compound at the point of the precipitation is not uniform with the concentration in bulk solution.

Applicant asserts that Szabo is not suitable for combination with Mittendorf because Szabo is drawn to injection in bolus dosages. However Szabo also teaches injection by infusions (page 820, 2nd paragraph under "Drugs.")

Applicant remarks that the compound disclosed by Mittendorf and the cannabinoid receptor agonists taught by Szabo are not equivalents because the compound of Mittendorf is structurally unrelated to the cannabinoid receptor ligands known so far, such as those taught by Szabo. However, the context of that statement is regarding ligands of the CB1 receptor, therefore the comparison is drawn to the pharmacological interaction of a compound and a specific receptor. In this regard, the instant compound is not structurally related to the moieties that result in receptor-binding in the prior art compounds. However, with regard to structural equivalence for determining solubility and formation of inclusion complexes with cyclodextrin, structural relationships are based on principles of physical organic chemistry, such as size of the molecule and polarity of the molecule. In this regard the compound disclosed by Mittendorf is a small organic molecule containing aromatic rings expected to form

inclusion complexes with cyclodextrin, as evidenced by Loftsson (Journal of Pharmaceutical Sciences, 1996, 85(10), p1017-1025, provided by Applicant in IDS filed 08 Oct 2004) page 1023, proposed structures of table 6 and table 7. Therefore one of ordinary skill in the art at the time of the invention would have a reasonable expectation that the compound disclosed by Mittendorf and the cannabinoid receptor agonists taught by Szabo possess similar physical organic characteristics. Further, Mittendorf discloses the compound with suitable excipients and envisions the use of organic solvents as auxiliary solvents if water is used as a diluent.

Claims 1- 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mittendorf et al. (US Patent 6,262,112, issued 17 Jul 2001, cited in PTO-892) in view of Szabo et al (J. Pharmacol. Exp. Ther., 2001) and Nakazi et al (Naunyn-Schmiedeberg's Arch. Pharmacol., 2000).

Mittendorf and Szabo teach as set forth above. The references are silent regarding the pH of the solutions or the use of citric acid.

Nakazi teaches that a citrate buffer (pH 4.8) is a suitable vehicle for cerebral infusion of the cannabinoid agonists, WIN 55,212-2 and CP 55,940. See paragraph bridging pages 20 and 21.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare a composition comprising said compound for infusion using any suitable physiologically solution for administration as taught by Mittendorf. One of ordinary skill would use a vehicle known to be used for other similar therapeutic

compounds, such as the aqueous solution comprising a cyclodextrin, with a reasonable expectation of success. In the absence of unexpected results, it would be further obvious to modify this composition by adjusting it to a suitable pH for cerebral infusion with a citrate buffer with a reasonable expectation of success.

The instant claims recite a composition comprising compound I and various standard physiological excipients. However, the examiner does not find there to be any evidence of criticality in any particular mix of components.

Claims 1-4 and 8-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mittendorf et al. (US Patent 6,262,112, issued 17 Jul 2001, cited in PTO-892) in view of Szabo et al (J. Pharmacol. Exp. Ther., 2001) and Yamada (US 5,807,337).

Mittendorf and Szabo teach as set forth above. The references teach the infusion of cannabinoid receptor agonists but are silent regarding the description of the infusion apparatus used in each reference.

It is well known in the art to use an infusion apparatus for the continuous administration of therapeutic agents, and the drug-contacting surfaces are typically plastic. See, for example, Yamada at col 5, lines 15-25.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare the recited composition, as set forth above. It would be further obvious to combine the composition with an infusion apparatus to form a kit for administration of the composition. It would be within the scope of the artisan to select any appropriate apparatus for this utility.

Conclusion

No claim is found to be allowable.

This Office Action details new grounds of rejection not necessitated by Applicant's Amendment. Accordingly, this Office Action is Non-Final.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jonathan S. Lau whose telephone number is 571-270-3531. The examiner can normally be reached on Monday - Thursday, 9 am - 4 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jonathan Lau
Patent Examiner
Art Unit 1623

/Shaojia Anna Jiang, Ph.D./
Supervisory Patent Examiner, Art Unit 1623